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THE EFFECT OF ANESTHETICS ON THE RESPIRATORY REFLEXES OF THE CAROTID SINUS

/Following is a translation of an article written by Tung Ch'uan-sheng (董泉聲) and Huang Chung-sun (黄仲蓀) Physiology Teaching-Research Staff, Chung King Medical College, in Sheng-li Hsueh-pao (Acta Physiologica Sinica), Peiping, Vol 24, No. 2, June 1960, pages 121-128./

In a previous paper (1) /numbers in parentheses refer to bibliographical entries/ we reported that when we stimulated the carotid sinus of slightly-anesthetized or wide-awake dogs, we found that respiration could have many characteristics, of which excitatory response is the most common. It was established that such responses are caused by the sensitivity of the carotid sinus being irritated, and not by the drop of blood pressure nor by the side effects induced by the body-chemical sense organs being stimulated. Aside from these observations, some other investigations have demonstrated that the respiratory response is fundamentally the same following sectioning of the vagus-pressor nerves as before the sectioning, although a small percent of animals show inhibitory response. We consider that these characteristics of response, namely excitatory vs. inhibitory, depend largely on the condition of the functions of the central nervous system. The factors that determine the condition of the functions of the central nervous system are many: the kind of anesthetic used, the depth of anesthesia and the transmissibility of the vagus-pressor nerves all have a certain effect. The animals used in the experiment on which this paper is based were dogs. In this recent experiment we made further observations and analyses of the sensitivity of the vagus-pressor nerves as reflected in the respiratory responses of dog under the influence of different anesthetic actions and different physiological conditions.

Method of Experimentation

This experiment called for 55 dogs. The main trunk of the vagus nerve of 46 of them was sectioned successfully. Six different kinds of anesthetics were used: (1) pentothal in 18 cases, the method of application being the same as in our previous experiment [1]; (2) amytal in six cases, intramuscular injection, 60-70 mg/kg; (3) sodium barbital in six cases, five of which were given pentothal first as anesthetic, then operated upon,

and upon regaining consciousness were given sodium barbital by intravenous injection to heighten the anesthesia; the dosages varied, the criterion being met when the animal no longer struggles upon being given painful stimulation; in one case morphine was first used to calm the animal (by subcutaneous injection, 3 mg/kg), then sodium barbital was administered; (4) in eight cases, penthobarbital was given by intravenous injection, 30-35 mg/kg; (5) in seven cases amyl-beta-butylic acid (氨基甲酸乙酯) was given by intravenous injection, 1.5-1.8 mg/kg.

The dogs that were given pentothal were often in light sleep, some were even wide awake. Chloralose anesthesia wore off easily also. The anesthetic action of pentobarbital was not long-lasting enough to suit our purpose either. The other three anesthetics have longer-lasting effects and produce deeper sleep, and are generally satisfactory for general purposes. But when we study the effect of the depth of anesthesia on respiratory responses we increase the amount whenever necessary.

In our studies of the stimulation of the carotid sinus we used either the method of inverting the venous sac (same as that used in our previous experiment[1] on 32 cases), or our improved method of increasing pressure at the blind end (in 23 cases). The latter method consists of insolating the carotid sinus and the membrane of the outer carotid artery between the occipital arteries from the adjoining muscles by means of a hemastat shaped like a mosquito with its proboscis at work, tying the neck artery at this junction, and finally tying the inner neck artery. Refer to Fig. 1 for an illustration of the pressor portion and the inverted venous sac method. /All figures are appended at end of text./

Results of Experiment

1. Effect of Carotid-sinus Pressure Stimulation on Respiration under the Influence of Different Anesthetics

The results of the experiment showed that the character of the respiratory response was generally the same in the animals whether they were under the anesthetic influence of penthobarbital, sodium barbital or sodium amytal, when the carotid sinus was stimulated. With the exception of a few cases of questionable indication, almost half of the responses were diphasic. The first phase consisted of a short, quick, (occupying about 2 or 3 respiration waves) and shallow inhibitory response. This occurred when the carotid sinus pressor was stimulated. The second phase, which followed the first immediately, was an excitatory response, showing principally deeper respiration, sometimes exhibiting the behavior of higher frequency. About one-half of the responses were excitatory (Fig 2, I). This confirms the findings of our previous investigation of the subject.

The responses in three of the eight cases anesthetized with pentobarbital were not clear. In three cases they were shallow and

definitely inhibitory. In two cases they were reinforced responses. In one case the respiration frequency was somewhat reduced in the initial period of pressor stimulation.

Of the ten cases of chloralose anesthesia, four were diphase responses. In three cases they were reinforced responses. In one case they and respiration were simultaneously reinforced and the respiration frequency was reduced somewhat. In three cases they were either indistinct or very shallow and short inhibitory responses (Fig 4, I).

Of the seven cases that were anesthetized with amyl-beta-butylic acid, the response in one was indistinct, in one response they were re-inforced, and in the remaining five all were shallow or distinctly inhibitory respiratory responses.

2. Effect of Depth of Anesthesia on Respiratory Responses

In 18 cases anesthetic was added in the process of the experiment. Observations were made just prior to and immediately following administration to see the changes of respiratory behavior. Of the 18 cases, seven were penthotal cases, four were pentobarbital, five were chloralose and two were amyl-beta-butylic acid. Following the increase of anesthesia, conditions were judged by corneal reflex, lash reflex or respiration frequency.

It was found that in the 18 cases referred to above, regardless of the kinds of anesthetics given them and the original character of their respiratory responses, the changes brought about by the increase of dosage were limited to the degree of respiratory response, in proportion to the dosage. Even when there was a distinct change in degree, this gradually decreased and finally disappeared. No change of respiratory response character was observed.

Apart from this, in the first stage of an experimenting process many animals did not show any respiratory response when the carotid sinus is stimulated, or if they do show some responses, such responses are very minor. Only after a certain length of time do they respond to stimulation. Such behavior is commonly observed when sodium amytal, sodium barbital, penthotal or amyl-beta-butylic acid is used as anesthetic. We inferred that injuries caused by surgery were possibly responsible for any induced respiratory response. Judging by the conditions under which respiratory responses occur, it seems that they have even a closer relationship with the depth of anesthesia.

3. Effect of Sectioned Vagus-Depressor on Respiratory Responses under Influence of Anesthetics

The sensitivity of carotid sinus pressor and respiratory responses very often undergo certain changes following sectioning of right and left vagus depressor. But these changes vary according to the kind of

anesthetic used.

The respiratory responses of animals anesthetized with penthotal, sodium amytal or sodium barbital are fundamentally the same following sectioning of the trunk of the right and left vagus nerve as prior to the sectioning. In some animals the reinforced behavior is even more obvious (Fig. 2). In a small number of experiments the reinforced respiratory response and the lowering of the respiration frequency appeared simultaneously.

The respiratory responses of two dogs under penthotal were inhibitory originally. This inhibitory responses became more conspicuous following sectioning of the right and left vagus nerves (Fig. 3). In two other cases the respiratory responses were originally inconspicuous, but following vagus nerve sectioning and after considerable experimentation, the animals exhibited responses of lower respiratory frequency. In another case, the respiratory responses manifested themselves in an increased radius and slightly lowered frequency. These responses became conspicuous following vagus nerve sectioning. In two more other cases, originally one had been giving light inhibiting responses, the other excitatory responses. Now they were making respiratory responses which had the character of lowered frequency and a slightly increased radius. Based on these facts, we can say that in animals under pentobarbital anesthesia carotid sinus stimulation following double vagotomy easily evokes inhibitory responses in respiration.

Of the ten cases of chloralose anesthesia, only six were given experimental vagotomy studies. Of those that had shown diphase responses, such responses were more noticeable after vagotomy. Those whose responses had been inconspicuous or were of the light and short inhibitory type, now exhibited diphase responses (Fig. 4). Of the diphase respiratory responses exhibited after vagotomy, the inhibiting process of the first phase is more conspicuous, playing the most important role in the entire process of response. These facts demonstrate that in the case of carotid sinus stimulation in animals under chloralose anesthesia, the respiratory responses evoked after vagotomy are beneficial to the development of the inhibiting process. It can be readily seen upon referring to Fig. 4, that the degree of respiratory response is in direct proportion to the intensity of stimulation.

Of the five cases of amyl-beta-butylic acid anesthesia, the change in the process of inhibitory response in four was much more profound following vagotomy. In one case the respiratory responses were excitatory, but when the carotid sinus was stimulated, while the responses were still excitatory, the respiration frequency was lower. This is to say, the respiratory responses of animals under amyl-beta-butylic acid become more and more inhibitory following vagotomy.

4. Determination of the Pressure Sensitivity of the Carotid Sinus and the Threshold of Respiratory Response to Stimulation

Many investigators have determined the minimum stimulation value

of depressor response induced by carotid sinus pressor [2-5]. On account of the difference in the constitution of animals it varies, but is within the range of 20-80 mm mercury. But as regards the pressure sensitivity of the carotid sinus and the minimum stimulation value necessary for modifying the respiratory responses, nothing has appeared in print. We have made some studies in this regard, using 18 animals under sodium amyltalm pentobarbital, and chloralose anesthesia and applying blind-end pressor stimulation. When the vagus nerves were intact the minimum pressure value required in the carotid sinus to induce respiratory responses, either excitatory or inhibitory, was between 100 mm and 160 mm mercury, 120-140 mm being most common. If stimulation was increased, the degree of respiratory response was correspondently increased. In the 18 animals mentioned above the stimulation threshold of depressor response was between 10 mm and 100 mm mercury, 60-80 mm being the most common. Following double vagotomy the respiratory responses were the same as the blood pressure responses, the stimulation threshold was somewhat lower in the majority of cases, and some animals required only 50-60 mm mercury to exhibit clear respiratory responses.

Discussion

As we all know, different anesthetics may have different effects on the central nervous system. Some reports [6,7] are available on the effect of different kinds of anesthesia on the depressor-sensitive responses of the carotid sinus and on the chemical-sensitive respiratory responses of the carotid body. But little is available in print on the effect of different anesthetics on the pressure-sensitive respiratory responses of the carotid sinus. Schmidt [8] has pointed out that barbitals tend to diminish pressure-sensitive respiratory responses, while morphine tends to increase the inhibitory respiratory responses. Dripps and Dumke [7] directly stimulated the fibers of the carotid sinus depressor of the medulla oblongata of dogs under chloralose with induction coil current and found that respiration exhibited no reaction to stimulation. In our experiment, when the carotid sinus of dogs under penthotal, sodium amytal, and sodium barbital was stimulated, the respiratory responses were mainly of an excitatory character. The responses of dogs under chloralose were generally similar to those just mentioned. Those of animals under penthotal were either inhibitory or excitatory, the former being dominant. However, those responses of the animals under amyl-beta-butylic acid were principally inhibitory in character. It is plain that the character of the pressure-sensitive respiratory responses of the carotid sinus because the anesthetics used were different.

It is unclear why different kinds of anesthetic change the character of the respiratory responses. Neil [9-11] found in his experiment on cats or dogs that chloralose added to penthotal stimulation of the vagus-depressor nerves or the side of the sinus nerve facing the brain could change the depressor responses into pressor responses, and if an additional

amount of penthotal was used to deepen the anesthesia, it could only induce repressor responses. He believes that one of the reasons is that chloralose reduces the sensitivity of the pressure-sensitive impulses of the central circulatory system, causing the impulses that have been transmitted by the chemical-sensitive fibers to appear clearly, resulting in the rise of blood pressure. Although the results of that experiment are not entirely in agreement with our observations, they nevertheless similarly point out that when the nervous system is under the influence of different anesthetics, similar stimulation can evoke reflexive responses of varied character.

Different anesthetics have inhibitory effects of different degrees on the activity of acetylcholinesterase in the central nervous system (12-13). Based on this fact the following is a plausible explanation of the phenomena we encountered. When different anesthetics are used, the amount of acetylcholinesterase in the central nervous system, which has some relation with respiration, varies in each case. So when similar stimulations are applied to the carotid sinus they evoke through the central nervous system different respiratory responses. But the trouble with this explanation is that certain other facts show that while there is a relation between the amount of acetylcholinesterase and the processes of transmission of excitatory activities in the central nervous system, they are not entirely determined by one single factor (14).

Like other tissues, the sensitivity of the cells of one part of the nervous system to drugs, including anesthetics, is not the same as that of cells of other parts. Many anesthetics have their own properties which are different from those of similar drugs. Up to now not enough is understood in regard to the nature of the action of different anesthetics on the central nervous system. Such being the case, the reason for the fact that different anesthetics produce different results in the pressure-sensitive respiratory responses of the carotid sinus requires further analytical study.

Some writers (15,16) believe that respiratory movements with respect to responses induced by stimulation of the pressure-sensitive sense organs of the carotid sinus are determined by whether or not the vagus-depressor nerve is complete. They believe that only after this nerve has been sectioned will inhibitory responses appear regularly. In our experiment on animals anesthetized with penthotal, sodium amytal and sodium barbital the respiratory responses following double vagotomy were similar to those of the above report. The excitatory responses of some animals were even more profound following sectioning of the trunk of the vagus nerves. But in cases where the animals were anesthetized with amyl-beta-butylic acid, penthotal and chloralose, sectioning of the vagus-depressor nerve caused respiration to develop toward inhibition or intensified inhibitory responses. It is clear that in the light of this that sectioning of the vagus-depressor nerve definitely effects or changes the pressure-sensitive respiratory responses of the carotid sinus, and that these changes vary on account of the different kinds of anesthesias used.

Heymans (17, 18) and Winder (16), in their experiment on dogs anesthetized with chloralose or amyl-beta-butylic acid whose vagus nerves had been sectioned, found that stimulation of the carotid sinus induced inhibitory responses in respiration. This is in general consistent with our findings.

In their experiment on rabbits anesthetized with amyl-beta-butylic acid, Chang Ching-ju (張鏡如) and Su Ch'ing-fen (蘇清芬) determined that the depressor nerve and the abdominal vagus nerve have no apparent relation with this kind of respiratory response, but that the removal of vagus nerves in the neck is advantageous to the development of inhibitory responses. It appears that the changes in respiration observed following sectioning of the trunk of the vagus nerve has generally some relation with the changes in the functional conditions of the respiratory center brought about by the loss of impulses transmitted by the sense organs in the lungs.

Deepening the anesthesia would gradually weaken or even stop the activities of the various reflexes. The findings we report in this paper with respect to respiratory responses and the characteristics of the relationship between general reflexes and the dosages of anesthetics are consistent. Namely, the deepening of anesthesia could weaken or even abolish respiratory responses; the original responses reappear gradually when the anesthesia becomes shallower and shallower. Based on these facts, we believe that it is not the depth of anesthesia that determines the character of the pressure-sensitive respiratory responses of the carotid sinus, and that the depth of anesthesia is only one important factor that causes quantitative changes in this kind of respiratory responses. Chang Ching-ju, et al, found that when morphine anesthesia was deepened, respiratory inhibition dominates. This, believes Chang, is possibly due to the special inhibitory action of morphine on the center of respiration, and not to any imaginative action that is common in all anesthetics.

When the anesthetic condition and the vagus nerves are normal, the stimulation threshold of the pressure-sensitive respiratory responses of the carotid sinus is usually between 120 mm and 140 mm mercury. This numerical value is close to the blood pressure of animals in experimental studies. Besides, the stimulation threshold drops following vagotomy. So this kind of respiratory response does not necessarily appear under high pressure in experimental processes. Under such conditions it is only the stimulation that is intensified and the respiratory responses that change more conspicuously. This is what makes some people imagine that the transmissive impulses of the carotid sinus regularly effect the center of respiration.

Based on the above-mentioned phenomena, we believe that the transmitting fibers of the carotid sinus develop relationships with the circulary and respiratory systems respectively. These relationships of a nervous origin have different characteristics both structurally and functionally. The functional conditions of the center of the nervous system change in accordance with environmental conditions, and therefore may, in combination with transmissive nervous impulses, develop divergent or even opposite responses to the circulary and respiratory centers.

Summary

The character of the respiratory responses induced by the pressure-sensitive sense organs when the carotid sinus is stimulated has a close relationship with the kind of anesthetics used. The respiratory responses of animals under penthotal, sodium amytal, and sodium barbital were principally excitatory. In animals under pentobarbital, there were more inhibitory responses than excitatory responses. In animals under chloralose, a majority of the respiratory responses were either excitatory or diphase in character. In animals under amyl-beta-butylic acid the responses were principally inhibitory in character.

The sectioning of the trunk of the right and left vagus nerves in the neck region can effect respiratory responses, but it has a definite relationship with the different kinds of anesthetics used. In animals anesthetized with penthotal, sodium amytal and sodium barbital, the responses were principally excitatory. Following sectioning of the trunk of the vagus nerve, the degree of excitation in some of these animals even became more conspicuous. In a small number of the animals the degree of excitation and respiration were reinforced simultaneously, while the respiratory frequency was lowered. In animals anesthetized with amyl-beta-butylic acid, penthotal, or chloralose, vagotomy proved advantageous to the strengthening or development of inhibitory responses.

Deepening of anesthesia could effect the degree of respiratory responses, but would not change the character of the respiratory responses.

The stimulation threshold of the pressure-sensitive respiratory responses of the carotid sinus was in most cases 120-140 mm mercury under our experimental conditions. The threshold value dropped somewhat following sectioning of the trunk of the vagus nerve.

As regards the effect of the different kinds of anesthetics and vagotomy on respiratory responses and the paths of transmission of the pressure-sensitive respiratory responses of the carotid sinus, discussion has been made in this paper.

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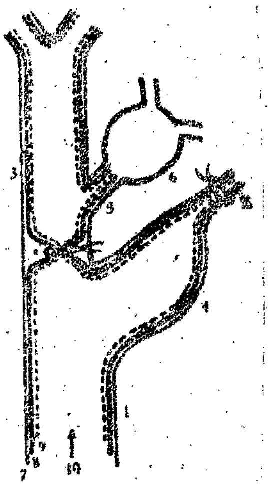
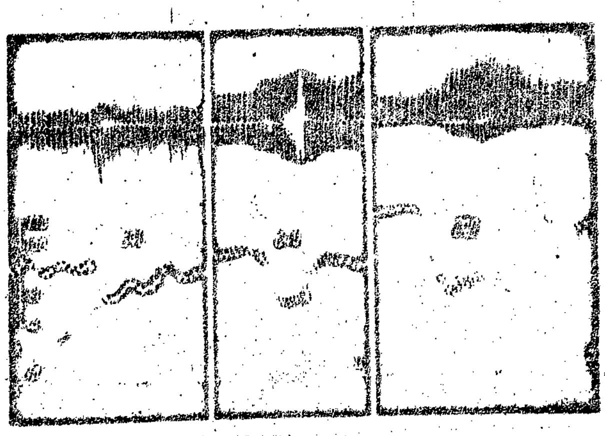
Fig. 1.



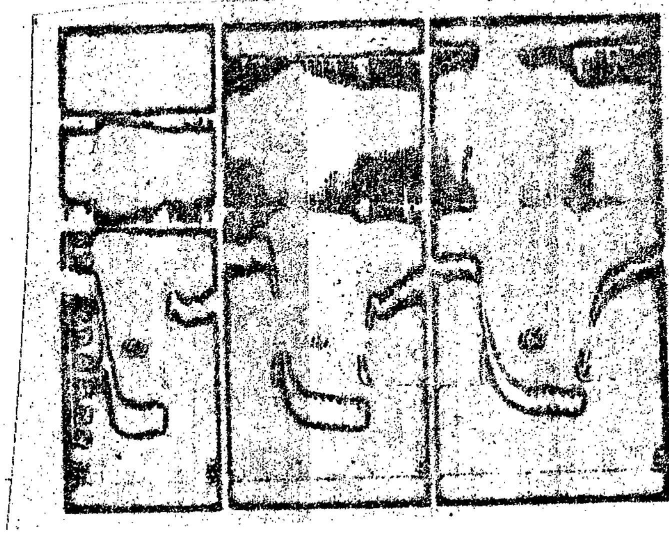
1. Main carotid artery
2. Internal carotid artery
3. External carotid artery
4. Carotid sinus sac
5. Occipital artery
6. Carotid artery sac
7. Inner membrane of arterial wall
8. Muscle layer of arterial wall
9. Inner membrane of arterial wall
10. Arrow pointing to carotid sinus sac

Fig. 2.



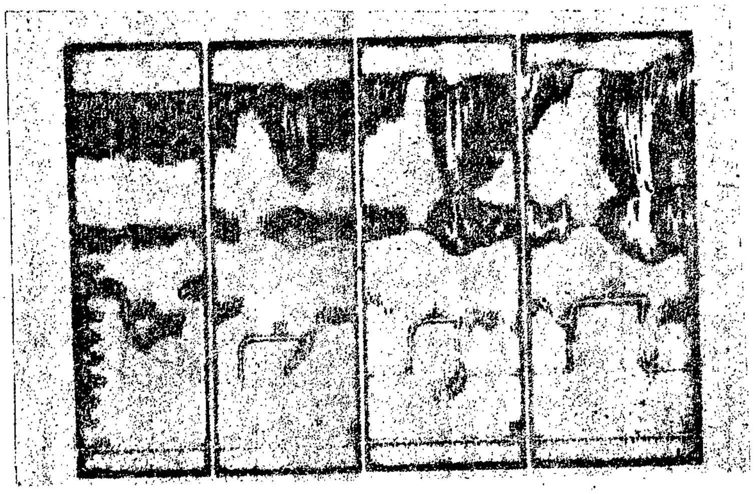
Dog, ♀, 13 kilograms, anesthetized with sodium amytal. Respiratory reactions to carotid sinus pressor stimulation, following sectioning of the vagus nerves. Inverted venous sac method pressor. Between I and II trunk of right vagus nerve sectioned. I, II and III: carotid sinuses (right and left) pressor 240 mm mercury. Curve from top to bottom: record of side-tube of respirator, arterial blood pressure, carotid sinus (r. & l.) stimulation marks, time marks.

Fig. 3.



Dog, ♂, 10.5 kilograms, anesthetized with pentobarbital. Blind-end method pressor. Between I and II and between II and III: trunk of right and left vagus nerves sectioned. I and II: Carotid sinuses, R. and l., pressor 160 mm mercury. Curve from top to bottom: Respiration as recorded by respiration recording instrument respiration as recorded by side-tube of respirator, arterial blood pressure, carotid sinus (r. & l.) stimulation marks, time marks).

Fig. 4.



Dog, ♀, 12 kilograms, anesthetized with chloralose. Blind-end method pressor. Between I and II: trunk of right and left vagus nerve sectioned. I, II, III and IV carotid sinuses, right and left, pressor 180 mm, 100 mm, 140 mm and 200 mm mercury, respectively. Curve: indications same as in Fig. 3.

Fig. 5.

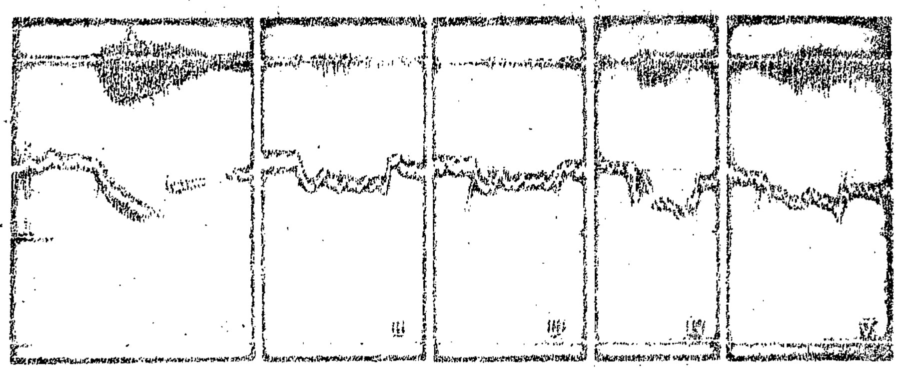


Fig. 5 shows the changes in a penthotal case. Inverted venous sac method. I, II, III, IV and V: Carotid sinus (r. & l.) pressor 240 mm mercury. Between I and II 2 mm of 2% penthotal injected intravenously to deepen anesthesia. II, III, IV and V: carotid sinus stimulation 2, 5, 6.5, 29, and 34 minutes, respectively, following injection of penthotal. I. corneal reflex sensitive, II, III corneal reflex disappeared. IV, V corneal reflex reappeared. Curve indications same as in Fig. 2.

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